| FORM PTO-1390 (REV 5-93) | U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE | ATTORNEY DOCKET NO. 101615-00012 |
|---|---|---|
| TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371 | | DATE: July 26, 2001 |
| | | U.S. APPLN. NO. (IF KNOWN, SEE 37 C.F.R. 1.5) Not Yet Assigned 09/786933 |

| INTERNATIONAL APPLICATION NO. | INTERNATIONAL FILING DATE | PRIORITY DATE CLAIMED |
|---|---|---|
| PCT/EP00/00957 | 7 February 2000 | 17 February 1999 |

TITLE OF INVENTION: ESSENTIAL FATTY ACIDS IN THE PREVENTION OF CARDIOVASCULAR EVENTS

APPLICANT(S) FOR DO/EO/US: Franco PAMPARANA

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371. (THE BASIC FILING FEE IS ATTACHED)
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures [35 U.S.C. 371(f)] at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☐ A proper demand for International Preliminary Amendment was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed [35 U.S.C. 371(c)(2)]
   a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English [35 U.S.C. 371(c)(2)].
7. ☒ Amendments to the claims of the International Application under PCT Article 19 [35 U.S.C. 371(c)(3)]
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 [35 U.S.C. 371(c)(3)].
9. ☒ An oath or declaration of the inventor(s) [35 U.S.C. 371(c)(4)].
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 [35 U.S.C. 371(c)(5)].

Items 11 - 16 below concern other document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98.
12. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information: ☒PCT/IPEA/409 ; PCT/IB/301; PCT/IB308; PCT/IB304; PCT/IB/332; PCT/RO/101; PCT/ISA/210

JC17 Rec'd PCT/PTO 26 JUL 2001

| U.S. APPL'N. NO. (IF KNOWN SEE 37 C.F.R. 1.5) 09/869333 | INTERNATIONAL APPLICATION NO. PCT/EP00/00957 | ATTORNEY DOCKET NO. 101615-00012<br>DATE: July 26, 2001 |
|---|---|---|

17. ☒ The following fees are submitted:

**Basic National Fee [37 C.F.R. 1.492(a)(1)-(5)]:**

Search Report has been prepared by the EPO or JPO.....$860.00
International preliminary examination fee paid to USPTO (37 C.F.R. 1.482).....$690.00
No international preliminary examination fee paid to USPTO (37 C.F.R. 1.482) but international search fee paid to USPTO [37 C.F.R. 1.445(a)(2)].....$710.00
Neither international preliminary examination fee (37 C.F.R. 1.482) or international search fee [37 C.F.R. 1.445(a)(2)] paid to USPTO.....$1,000.00
International preliminary examination fee paid to USPTO (37 C.F.R. 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4).....$ 100.00

| CALCULATIONS | PTO USE ONLY |
|---|---|

| | | | | | |
|---|---|---|---|---|---|
| **ENTER APPROPRIATE BASIC FEE AMOUNT =** | | | | $ 860.00 | |
| Surcharge of $130.00 for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date [37 C.F.R. 1.492(e)]. | | | | $ 0.00 | |
| Claims | Number Filed | Number Extra | Rate | | |
| Total Claims | 29 - 20 = | 9 | X $ 18.00 | $ 162.00 | |
| Independent Claims | 6 - 3 = | 3 | X $ 80.00 | $ 240.00 | |
| Multiple dependent claim(s) (if applicable) | | | + $270.00 | $ 0.00 | |
| **TOTAL OF ABOVE CALCULATIONS =** | | | | $ 1,262.00 | |
| Reduction by one-half for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 C.F.R. 1.9, 1.27, 1.28). - | | | | $ 0.00 | |
| **SUBTOTAL =** | | | | $ 1,262.00 | |
| Processing fee of $130.00 for furnishing the English translation later the ☐ 20 ☐ 30 months from the earliest claimed priority date [37 C.F.R. 1.492(f)]. + | | | | $ 0.00 | |
| **TOTAL NATIONAL FEE =** | | | | $ 1,262.00 | |
| Fee for recording the enclosed assignment [37 C.F.R. 1.21(h)]. The assignment must be accompanied by an appropriate cover sheet (37 C.F.R. 3.28, 3.31). $40.00 per property + | | | | $ 40.00 | |
| **TOTAL FEES ENCLOSED =** | | | | $ 1,302.00 | |
| | | | | Amount to be refunded | $ |
| | | | | Charged | $ |

a. ☒ A check in the amount of $1,302.00 to cover the above fees is enclosed.
b. ☐ Please charge my Deposit Account No. 01-2300 in the amount of $ to cover the above fee. A duplicate copy of this sheet is enclosed.
c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 01-2300.

NOTE: Where an appropriate time limit under 37 C.F.R. 1.494 or 1.495 has not been met, a petition to revive [37 C.F.R. 1.137(a) or (b)] must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:
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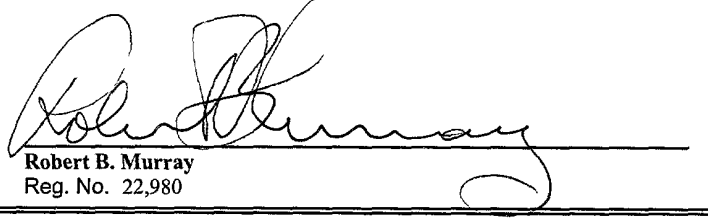
**Tel: (202) 857-6000 Fax: (202) 638-4810**
RBM/aam



**Robert B. Murray**
Reg. No. 22,980

**PATENT APPLICATION**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:

PAMPARANA, Franco

Group Art Unit: Unknown

Application No.: Not Yet Assigned

Examiner: Unknown

Filed: Concurrently herewith

Attorney Dkt. No.: 101615-00012

For: ESSENTIAL FATTY ACIDS IN THE PREVENTION OF CARDIOVASCULAR EVENTS

**PRELIMINARY AMENDMENT**

Commissioner for Patents
Washington, D.C. 20231

Date: July 26, 2001

Sir:

Prior to initial examination of the application, please amend the above-identified application as follows:

**IN THE CLAIMS**:

Please amend claims 1, 3-5, 9-11, 15, 21, 26, and 29 as follows:

1. (Amended) Use of essential fatty acids containing a mixture of eicosapentaenoic acid ethyl ester (EPA) and docosahexaenoic acid ethyl ester (DWA) in the preparation of a medicament useful for preventing mortality in a patient who has suffered from a myocardial infarction where the content in EPA+DWA in such mixture is greater than 25% b.w.; and the medicament is for oral administration

3. (Amended) Use according to claim 1, wherein the content in EPA+DHA in such mixture is about 30 to about 100% b.w.

4. (Amended) Use according to claim 1, wherein the content in EPA+DHA in such mixture is about 85% b.w.

5. (Amended) Use according to claim 4, wherein the medicament is for oral administration, at a dosage from about 0.7g to about 1.5g daily.

9. (Amended) Use according to claim 7, wherein the EPA or EHA content is from about 60 to about 100% b.w.

10. (Amended) Use according to claim 8, wherein the EPA or EHA content is from about 60 to about 100% b.w.

11. (Amended) Use according to claim 8, wherein the medicament is for oral administration.

15. (Amended) A method according to claim 12, wherein the medicament is administered orally.

21. (Amended) A method according to claim 18, wherein the medicament is administered orally.

26. (Amended) A method according to claim 24, wherein the medicament is administered orally.

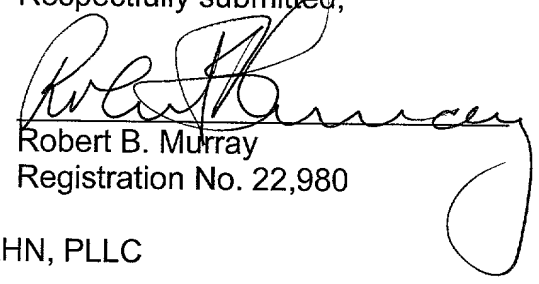
29. (Amended) A method according to claim 27, wherein the medicament is administered orally.

**REMARKS**

Claims 1-29 are pending in this application. By this Amendment, claims 1, 3-5, 9-11, 15, 21, 26, and 29 are amended to delete multiple dependency. No new matter is contained in the amendments.

Please charge any fee deficiency or credit any overpayment to Deposit Account No. 01-2300.

Respectfully submitted,



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RBM/gck

## MARKED-UP ORIGINAL CLAIMS

1. (Amended) Use of essential fatty acids containing a mixture of eicosapentaenoic [eicosapentanoic] acid ethyl ester (EPA) and docosahexaenoic acid ethyl ester (DWA) in the preparation of a medicament useful for preventing mortality in a patient who has suffered from a myocardial infarction where the content in EPA+DWA in such mixture is greater than 25% b.w.; and the medicament is for oral administration

3. (Amended) Use according to claim 1 [or 2], wherein the content in EPA+DHA in such mixture is about 30 to about 100% b.w.

4. (Amended) Use according to claim 1[or 2], wherein the content in EPA+DHA in such mixture is about 85% b.w.

5. (Amended) Use according to claim 4[1], wherein the medicament is for oral administration, at a dosage from about 0.7g to about 1.5g daily.

9. (Amended) Use according to claim 7 [or 8], wherein the EPA or EHA content is from about 60 to about 100% b.w.

10. (Amended) Use according to claim 8 [or 9], wherein the EPA or EHA content is from about 60 to about 100% b.w.

11. (Amended) Use according to [anyone of claims 8 to 10] claim 8, wherein the medicament is for oral administration.

15. (Amended) A method according to claim 12 [13 or 14], wherein the medicament is administered orally.

21. (Amended) A method according to claim 18, [19 or 20] wherein the medicament is administered orally.

26. (Amended) A method according to claim 24 [or 25], wherein the medicament is administered orally.

29. (Amended) A method according to claim 27 [or 28], wherein the medicament is administered orally.

"ESSENTIAL FATTY ACIDS IN THE PREVENTION OF CARDIOVASCULAR EVENTS"

DESCRIPTION

This invention concerns the use of a pharmaceutical composition containing essential fatty acid ethyl esters originating from fish oils, in particular as a high concentration mixture of ethyl esters of (20:5ω 3) eicosapentaenoic acid (EPA) and (22:6ω 3) docosahexaenoic acid (DHA) in the prevention of cardiovascular events, especially of mortality in patients who have survived the hospitalization phase of acute myocardial infarction (AMI).

It is well known that certain essential fatty acids contained in fish oil have a therapeutic effect in the prevention and treatment of cardiovascular disorders, such as in the treatment of thrombosis, hypercholesterolemia, arteriosclerosis, cerebral infarction and hyperlipemias.

U.S. Patents US 5,502,077, US 5,656,667 and US 5,698,594 can be quoted as examples.

From the above prior art, it is known in particular the utility of fatty acids belonging to the ω-3 family, more specifically (20:5ω 3) eicosapentaenoic acid (EPA) and (22:6ω 3) docosahexaenoic acid (DHA) in treating the above-mentioned disorders.

Indeed EPA, being a precursor of PGI3 and TxA3, exerts a preventing platelet aggregation effect and an antithrombotic effect that can be ascribed to inhibition of cyclooxygenase (similar effect to that of aspirin) and/or to competition with arachidonic acid for this enzyme, with consequent reduction in the synthesis of PGE2 and TxA2, which are well known platelet aggregating agents.

On the other hand DHA is the most important component of cerebral lipids in man and furthermore, being a structural component of the platelet cell,

it intervenes indirectly in increasing platelet fluidity, thus playing an important role in antithrombotic activity.

International patent application W089/11521, whose description is herein incorporated by reference, describes in particular an industrial process for extracting mixtures with a high content in poly-unsaturated acids, including EPA and DHA and their ethyl esters, from animal and/or vegetable oils.

Mixtures of fatty acids, especially EPA/DHA, obtained according to W089/11521, are reported to be particularly useful in the treatment of cardiovascular diseases.

However, currently used treatments in human therapy have been shown to be insufficient in preventing cardiovascular events, and more specifically mortality, in particular due to sudden death, which happen in patients who have had a myocardial infarction, on account of recurrences after a first acute myocardial infarction episode.

Therefore, there still is the need for an effective drug, in particular for preventing these recurrences.

Object of this invention, therefore, is the use of essential fatty acids with a high content in EPA-ethyl ester or DHA-ethyl ester or a high concentration mixture thereof, in the preparation of a medicament useful for preventing mortality, due, for instance, to cardiovascular events or sudden death, in patients who have suffered from a myocardial infarction.

According to a preferred aspect this invention therefore provides the use of essential fatty acids with a high content in EPA-ethyl ester or DHA-ethyl ester or a high concentration mixture thereof, in the preparation of a medicament useful for preventing sudden death in patients who have suffered from a myocardial infarction.

For ease of description "EPA-ethyl ester" and "DHA-ethyl ester" will be also quoted here as "EPA" and "DHA".

An essential fatty acid with high content in EPA-ethyl ester or DHA-ethyl

ester, according to the present invention, preferably contains more than 25% by weight (b.w.), in particular from about 60 to about 100% of such ester.

These compounds can be obtained by known methods.

In an essential fatty acid with a high concentration mixture of EPA-ethyl ester and DHA-ethyl ester, preferably such mixture has a content in EPA + DHA greater than 25% by weight, in particular from about 30 to about 100% by weight, preferably about 85% by weight.

In the EPA/DHA mixture, EPA preferably is present in a percentage from about 40 to about 60% by weight and DHA, preferably in a percentage from about 25 to about 45-50%.

In any case the preferred EPA/DHA ratio in such EPA/DHA mixture is about 0.9/1.5.

PHARMACOLOGY

The efficacy of the treatment, according to the invention, is, for instance, proven by the fact that a surprising and highly significant reduction in post-infarction mortality was observed by such treatment in a clinical trial that lasted for 3.5 years, with protocols substantially designed as follows:

1 a "control " group received the standard therapy which is usually given to infarcted patients;

2 a "treatment" group, besides the therapy that was given to the "control" group, received 85% EPA+DHA (1 g daily);

3 a "treatment" group, besides the therapy that was given to the "control" group received vitamin E; and

4 a "treatment" group, besides the therapy that was given to the control group, received vitamin E and 85% EPA+DHA (1 g daily).

In fact the group of patient "treated" according to protocol 2 showed, in comparison to "control" group 1, a decrease of about 20% in total

mortality, with a decrease of about 40% of mortality due to sudden death and a notable reduction in mortality due to other cardiovascular events.

On the contrary, no significant results were achieved in group 3 as compared to the control group 1, whereas there was a reduction in total mortality of about 19% in group 4 as compared to the control group, with results that were similar to those obtained in treated group 2.From the above clinical results, the person skilled in the art will appreciate that, the use of a pharmaceutical composition in accordance to the present invention is certainly useful in human therapy in preventing mortality in patients who have suffered from a myocardial infarction.

Accordingly, this invention provides a method for preventing mortality in a patient who has survived a myocardial infarction, comprising administering to such patient a therapeutically effective amount of a medicament containing essential fatty acids with a high content in EPA-ethyl ester or DHA-ethyl ester or a high concentration mixture thereof.

As known, sudden death is an important contributor to the mortality rate in patients with cardiac disease, accounting for over 450,000 death per year in the USA.

About 80% of such patients, particularly those survivors of acute myocardial infarction with low ventricular ejection fractions, are at high risk of sudden death or reinfarction.

The above clinical results show that the present invention provides a new and valuable therapeutic tool for preventing sudden death in patients in particular in those who survived acute myocardial infarction.

Accordingly, as a preferred aspect, the present invention also provides a method for preventing sudden death in a patient, who is survivor of myocardial infarction, comprising administering to such patient a therapeutically effective amount of a medicament containing essential fatty acids with a high content in EPA-ethyl ester or DHA-ethyl ester or a high concentration mixture thereof.

The essential fatty acids, according to the invention, can either have a high content, for instance more than 25% b.w., in EPA-ethyl ester or DHA-ethyl ester or in a mixture thereof. However EPA-ethyl ester and DHA-ethyl ester are preferably present as a mixture thereof with a content in EPA+DHA higher than 25% b.w, in particular from about 30 to about 100% b.w., preferably about 85% b.w.

Based on the obtained clinical results, according to a preferred aspect of the invention, the dosage of an essential fatty acid containing a EPA+DHA mixture with 85% b.w. titer for oral administration to a patient may vary from about 0.7 g to about 1.5 g daily, preferably about 1 g daily.

This amount of product as EPA+DHA mixture (or amount of EPA-ethyl ester alone or DHA-ethyl ester alone) may be administered in several divided doses throughout the day or preferably in a single administration, in order to achieve the desired hematic level. Obviously it is at the discretion of the physician to adjust the quantity of product to be administered according to the age, weight and general conditions of the patient.

The medicament, e.g. in the form of a pharmaceutical composition, according to this invention can be prepared according to known methods in the art. The preferred route of administration is the oral one, however leaving alternative routes of administration, such as the parenteral route, to the discretion of the physician.

The following examples illustrate preferred formulations for oral administration, but do not intend to limit the invention in any way.

Gelatin capsules

According to known pharmaceutical techniques, capsules having the composition below and containing 1 g of active ingredient (EPA + DHA, 85% titer) per capsule are prepared.

Formulation 1

| | |
|---|---|
| EPA-ethyl ester | 525 mg/capsule; |
| DHA-ethyl ester | 315 mg/capsule; |
| d-alpha tocopherol | 4 IU/capsule; |
| gelatin | 246 mg/capsule |
| glycerol | 118 mg/capsule; |
| red iron oxide | 2.27 mg/capsule; |
| yellow iron oxide | 1.27 mg/capsule |

Formulation 2

| | |
|---|---|
| Ethyl esters of poly- | |
| unsaturated fatty acids | 1000 mg |
| with content in ethyl esters | |
| of ω-3 poly-unsaturated esters | |
| (eicosapentaenoic EPA , | |
| docosahexaenoic (DHA) | 850 mg |
| d-1-α tocopherol | 0.3 mg |
| gelatin succinate | 233 mg |
| glycerol | 67 mg |
| sodium p-oxybenzoate | 1.09 mg |
| sodium propyl p-oxobenzoate | 0.54 mg |

AMENDED CLAIMS

1. Use of essential fatty acids containing a mixture of eicosapentanoic acid ethyl ester (EPA) and docosahexaenoic acid ethyl ester (DHA) in the preparation of a medicament useful for preventing mortality in a patient who has suffered from a myocardial infarction where the content in EPA+DHA in such mixture is greater than 25% b.w; and the medicament is for oral administration.

2. Use according to claim 1, wherein the medicament is useful for preventing mortality due to sudden death in a patient who has suffered from a myocardial infarction.

3. Use according to claim 1 or 2, wherein the content in EPA+DHA in such mixture is from about 30 to about 100% b.w.

4. Use according to claim 1 or 2, wherein the content in EPA+DHA in such mixture is about 85% b.w.

5. Use according to claim 4, wherein the medicament is for oral administration, at a dosage from about 0.7 g to about 1.5 g daily.

6. Use according to claim 5, wherein the EPA/DHA ration in the EPA+DHA mixture is about 0.9/1.5.

7. Use of essential fatty acids containing eicosapentaenoic acid ethyl ester (EPA) or docosahexaenoic acid ethyl ester (DHA) in the preparation of a medicament useful for preventing mortality in a patient who has suffered from a myocardial infarction, wherein the EPA or DHA content is greater than 25% b.w.; and the medicament is for oral administration.

8. Use according to claim 7, wherein the medicament is useful for preventing mortality due to sudden death in a patient who has suffered from a myocardial infarction.

9. Use according to claim 7 or 8, wherein the EPA or DHA content is from about 60 to about 100% b.w.

N, M, M & O Docket No. _____ NIKAIDO, MARMELSTEIN, MURRAY & ORAM LLP

# Declaration For U.S. Patent Application

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled
(Insert Title) ESSENTIAL FATTY ACIDS IN THE PREVENTION OF CARDIOVASCULAR EVENTS

the specification of which is attached hereto unless the following box is checked:

☒ was filed on February 7, 2000 as United States Application Number or PCT International Application Number PCT/EP00/00957 and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claim(s), as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. §1.56.

I hereby claim foreign priority benefits under 35 U.S.C. §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below any foreign application for patent or inventor's certificate or PCT International Application having a filing date before that of the application(s) for which priority is claimed:

| (List prior foreign applications. See note A on back of this page) | (Number) | (Country) | (Day/Month/Year Filed) | Priority Claimed |
|---|---|---|---|---|
| | MI99A000313 | Italy | 17/02/1999 | ☒ Yes ☐ No |
| | | | | ☐ Yes ☐ No |
| | | | | ☐ Yes ☐ No |

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below.

| (Application Number) | (Filing Date) |
|---|---|
| | |
| | |

(See Note B on back of this page) ☐ See attached list for additional prior foreign or provisional applications.

I hereby claim the benefit under 35 U.S.C. §120 of any United States application(s) or §365(c) of any PCT International application(s) designating the United States of America listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior application(s) (U.S. or PCT) in the manner provided by the first paragraph of 35, U.S.C. §112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. §1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

| (List prior U.S. Applications or PCT International applications designating the U.S.) | (Application Serial No.) | (Filing Date) | (Status) (patented, pending, abandoned) |
|---|---|---|---|
| | | | |
| | | | |

13

And I hereby appoint as principal attorneys David T. Nikaido, Reg. No. 22,663; Charles M. Marmelstein, Reg. No. 25,895; George E. Oram, Jr., Reg. No. 27,931; Robert B. Murray, Reg. No. 22,980; Martin S. Postman, Reg. No. 18,570; E. Marcie Emas, Reg. No. 32,131; Michael G. Gilman, Reg. No. 19,114, Douglas H. Goldhush, Reg. No. 33,125; Kevin C. Brown, Reg. No. 32,402; Monica Chin Kitts, Reg. No. 36,105; Sharon N. Klesner, Reg. No. 36,335; John R. Fuisz, Reg. No. 37,327; and Richard J. Berman, Reg. No. 39,107.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

(See Note C on back of this page)

Full name of sole or first ~~inventor~~ inventor FRANCO PAMPARANA

Inventor's signature _____ July 10, 2001 Date

Residence Piazza Firenze, 19 - 20100 Milano (Italy) ITX

Citizenship Italy

Post Office Address Same as above